REMARKS

I. Claim Rejections-35 U.S.C. § 112

Claims 1, 5, 6, 9-11, and 15 were rejected under 35 U.S.C § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiner states the specification has differing meanings for the term "peptide." On page 9, it reads "peptide is arbitrarily defined as a peptide chain having a single peptide bond." However, on pages 15 and 16, Table 1, and other places, peptide is used in its usual sense to mean a few amino acids linked with peptide bonds, such as bradykinin or a five amino acid sequence called a peptide. The use of the term "peptide" is contradictory throughout the specification and the claims which leads to confusion as to the scope of the claims. Under one usage, no peptides are present in the independent claims, under another usage BK and its derivatives are peptides. Further, both contradictory usages appear to be supported by the specification. The Examiner further states that the issue would be moved if Applicant cancelled the claims directed only to "peptide" such as claim 1. Claim 3, which has specific peptides, is definite since the peptides are defined.

"The patentee may be his or her own lexicographer." Finnigan Corp v. International Trade Comm'n 180 F.3d 1354, 1364, 51 USPQ 2d 1001 (Fed. Cir. 1999). This is especially true for patents dealing with complicated technologies. "Varied use of a disputed term in the written description demonstrates the breadth of the term rather than providing a limited definition." Johnson Worldwide Associates, Inc. vs. Zebco Corp., 175 F.3d 985, 991 (Fed. Cir. 1999). In Pitney Bowes, Inc. vs. Hewlett-Packard Co., the word "spot" was used in the specification 44 times, however, two usages of "spot" in two occurrences resulted in a dispute as to its interpretation. The Federal Circuit reversed, finding that the context supported a different

interpretation for the last two usages." Pitney Bowes, Inc. v. Hewlett-Packard Co., 182 F.3d 1298, 1310, 51 USPQ 2d 1161, 1169 (Fed. Cir. 1999).

The court noted that a patent's written description can set forth more than one definition of a claim term. Id. at 1310. The Court concluded, "where the language of the written description is sufficient to put a reader on notice of the different uses of a term, and where those uses are further apparent from publicly-available documents referenced in the patent file, it is appropriate to depart from the normal rule of construing seemingly identical terms in the same manner." Id. at 1311. "[T]he term must be read to correspond to the only plausible meaning in each context." Id. Thus, following the canon of construction, while claims are to be construed in light of the specification, they are not necessarily limited by the specification. Enercon Gmbh v. International Trade Comm.'n, 151F. 3d, 1376, 1384 (Fed. Cir. 1998). The word peptide in the specification should be read in its context. One ordinarily skilled reading the word "peptide" in the specification would be put on notice as to what meaning it has. Additionally, reading the word "peptide" in the claims, in light of the specification in its context would put an ordinarily skilled person on notice of the meaning of the term "peptide." Therefore, Applicants respectfully request Examiner to withdraw this rejection.

II. Claim Rejections-35 U.S.C. § 102

Claims 1, 5, 6, 10, 11, 15, and 16 were rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Groves et al. The Examiner states the claims are directed to a one-step method of intravenously administering from 20-500 μg/kg of a peptide, oligopeptide, or protein or L-arginine, containing an arginine available to NOS, to a mammal in order to regulate NO production. Groves et al. disclose the one-step method of the intravenous administration of a regulator of NO production, HOE-140, a bradykinin B2 receptor administering a NO-regulating

amount of an peptide. Bradykinin, an arginine containing peptide, stimulates the production of NO and vasodilation, while the peptide HOE-140, which is a known bradykinin antagonist which contains arginine, limits NO production. The dosage is 200 μg/min for 15mins. If one assumes that the average weight of a patient is a180lbs, this is a dosage of about 36 μg/kg, which is well within Applicant's claimed range. Applicants respectfully traverse this rejection. "[T]o constitute in anticipation, all material elements recited in a claim must be found in one unit of prior art." Application of Marshall, 578 F.2d 301, 304 (1978)(citing Soundscriber Corp. v. United States, 360 F.2d 954, 960 (1966)). Pursuant to Application of Marshall, the CCPA held "it was error to reject claims of weight control process on grounds of anticipation where the primary reference did not disclose every element of the claimed subject matter in that it taught use of the drug to treat various conditions but did not even remotely suggest using the drug to lose weight." Marshall, at 304. In Marshall, the primary reference, the PDR, did not disclose every element of the claimed subject matter. Applicant claims were directed to a weight control process using an effective amount of the anesthetic, oxethazaine, to inhibit the release of the pancreatic secretory hormones, secretin, and pancreozymin, in order to control weight. Conversely, the Court stated, the PDR taught using drugs containing the anesthetic oxethazaine to inhibit release of the acid-stimulating, hormone, gastrin, in order to treat esophagitis, gastritis, peptic ulcer and irritable colon syndrome. The Court concluded, nothing in the PDR remotely suggested taking oxethazaine to lose weight and if anyone ever lost weight by following the PDR teachings, it was an unrecognized accident. "An accidental or unwitting duplication of an invention cannot constitute an anticipation." Marshall at 304 (citing In re Felton, 484 F.2d 495, 500, 179 USPQ 295, 298 (Cust. & Pat. App. 1973)). Similarly, Groves et al. fails to teach every material element of the claimed subject matter. As stated by the Examiner Groves et al. discloses

a method of administering a regulator of NO production, HOE-140, a bradykinin B2 receptor antagonist to a human. However, nothing in Groves et al. suggests a method of stimulating or inhibiting NOS for prevention or treatment of certain nitric oxide-mediated pathogenic conditions. Reading the claims in light of the specification, such pathogenic conditions are ischemic stroke, diabetes, systemic hypotension, multiple sclerosis, Huntington's disease, Parkinson's disease, Alzheimer's disease, and the like (See page 15 of specification). Therefore, if anyone prevented or treated some of the nitric oxide-mediated pathogenic conditions stated above following the teachings of Groves et al., it would be an unrecognized accident of the claimed invention. Such accidental duplications cannot constitute anticipation. Thus, Applicants respectfully request Examiner to withdrawal this rejection.

Claims 1, 5, 9-11, and 15 were rejected under 35 U.S.C. § 102(b) as being anticipated by Thiemermann et al. The Examiner states the claims are directed to a one-step method of intravenously administering from 20-500 μg/kg of a peptide, oligopeptide, or protein, containing an arginine available to NOS, to a mammal in order to regulate NO production. Thiemermann et al. discloses administration of 1-30 μg/kg of NO_2-Arg-L-arginine and other dipeptides containing arginine, in vivo, to rats raises blood pressure (vasoconstrictors). The Examiner asserts this is the same one-step method as claimed. The Applicants respectfully traverse this rejection. As stated above, for prior art to anticipate under 35 U.S.C. § 102, all material elements recited in a claim must be found in one unit of prior art. Marshall at 304 (citing Soundscriber Corp. at 960). There is no anticipation by Thiemermann et al. Applicants claims are directed to a method of administering from about 20-500 μg/kg of a peptide, oligopeptide, protein or L-arginine to stimulate or inhibit nitric oxide synthase for the prevention or treatment of certain nitric oxide-mediated pathogenic conditions (See claim 1). Similarly, claim 10 reads on a method of

preventing a disease or condition effected by stimulation or inhibition of nitric oxide synthase by administering from about 20-500μg/kg of a peptide, oligopeptide, protein, or L-arginine that acts as a substrate for or an inhibitor to nitric oxide synthase. Nothing in Thiemermann suggests taking a peptide, oligopeptide, protein, or L-arginine to act as a substrate for or inhibitor to nitric oxide synthase for the prevention or treatment of nitric oxide-mediated pathogenic conditions. In fact, Thiemermann, teaches the administration of NO_2Arg-Phen, Ala-NO_2Arg, or NO_2Arg-L-arginine which produced increases in mean arterial blood pressure but prevented co-infusion of L-arginine or their parent peptides. (See page 31, Abstract). Thus, not only does Thiemermann et al. fails to teach every material element of the claimed invention, it teaches away from the claimed invention. Applicants respectfully request Examiner to withdrawal this rejection as to claims 1, 5, 6, 9-11, and 15.

Claims 1, 3, 5, 6, 9-11, 15 and 16 were rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. 4585757[A]. The Examiner states U.S. 4585757 discloses the administration of arginine-containing peptides, CIP fragment, contraceptive tetrapeptide, and bradykinin in the range of 50-500μg/kg to lower blood pressure (Table 2 and 3). Pursuant to Application of Marshall, there is no anticipation. Like Marshall, Pang et al. does not disclose every material element of the claimed subject matter. Pang et al. teaches a composition comprising a peptide having the structure X-Y, Y-X, or a salt thereof. Additionally, Pang et al. teaches a method of alleviating hypertension. While Pang et al. suggests the administration of an arginine, and a peptide, nothing in Pang et al. suggests taking these compositions to alleviate as substrates to or inhibit nitric oxide synthase to treat or prevent nitric oxide-mediated pathogenic conditions. Pang's focus is decreasing blood pressure. If anyone ever treats or prevents a nitric oxide-mediated pathogenic condition by following Pang et al. it is an unrecognized accident.

Moreover, Pang et al. renders the present invention non-enabling. Pang et al. discloses the use of peptides having different amino acids structures (see column 6, lines 24-34). However, most of these amino acid sequences do not have at least one sterically accessible arginine moiety available. While the present invention is not limited to the use of any specific peptide, oligopeptide, or protein as a substrate, preferred substrates have one or more arginine groups available to the nitric oxide synthase. The amino acid compositions in Pang et al. are at most 4 amino acid residues long, where in many cases you do not have the x and the ω amino acids being arginine. The majority of amino acid compositions disclosed in Pang et al. with no accessible arginine group would show no affinity with nitric oxide synthase because nitric oxide synthase would not react on them, thus rendering the invention non-enabling. Therefore, Pang et al. under §102, not only fails to disclose every material element pursuant to Application of Marshall, but also renders the invention non-enabling. Applicants respectfully request Examiner to withdrawal this rejection.

Claims 1, 3, 5, 6, 9-11, 15, and 16 were rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. 6143719[A]. The Examiner states U.S. 6143719, by Schmaier, et al. discloses the intravenous administration in rabbits of SEQ ID NO: 19, which is the same sequence as Applicant's SEQ ID NO: 5 in Example 3, column 19-20. Although this reference is silent with regard to the effect of the peptide on nitric oxide synthase, since the recipient; compound administered; mode of administration; and amounts are the same, the result would inherently be the same as the claimed result. Applicants respectfully traverse this rejection.

Pursuant to Application of Marshall, there is no anticipation. Like Marshall, Schmaier et al. does not disclose every material element of the claimed subject matter. The claims of the present invention are directed to treatment or prevention of nitric oxide-mediated pathogenic

conditions. Applicants use an effective amount of a peptide, oligopeptide, protein, or L-arginine that acts as a substrate or inhibitor to nitric oxide synthase whereby the tertiary structure of the peptide, oligopeptide, or protein has one or more arginine groups available to the nitric oxide synthase. Schmaier, however, claims a method of inhibiting thrombin-induced platelet or other cell activation by administering a peptide that inhibits thrombin activation of platelets or other cells. Nothing in Schmaier suggests taking a peptide to treat or prevent certain nitric oxide-mediated pathogenic conditions. If anyone was cured of ischemic stroke, diabetes, systemic hypotension, multiple sclerosis, Huntington's disease, Parkinson's disease, or Alzheimer's disease, and the like, following the teachings of Schmaier et al., it was an unrecognized accident. An accidental or unwitting duplication of an invention cannot constitute anticipation. Marshall at 303 (citing In re Felton at 500).

Moreover, the general rule is that inherency may be relied upon where and only where the consequence of following the reference disclosure always inherently produces or results in the claimed invention. See W.L. Gore Associates Inc. v. Garlock Inc., 220 USPQ 303, 314 (Fed. Cir. 1983), cert. denied, 469 US 851 (1984). "Inherency may not be established by probabilities or possibilities regarding what may have resulted in the prior art." In re Oelrich, 666 F.2d 578, 212 USPQ 323, 326 (CCPA 1981). "[A]n examiner who relies on the theory of inherency 'must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art.'" Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Int. 1990). It would not be reasonable to assume that the administration of SEQ ID NO: 19 at a dosage of 3g/70Kg of body weight, because it has the same sequence as Applicants' SEQ ID NO: 5 would have the same result on NO production as in the claimed invention. The fact that a certain thing may result from a given

set of circumstances is not sufficient. The unstated element must exist as a matter of scientific fact and flow naturally from the elements expressly disclosed in the prior art reference. The claimed range is from about 20-500µg/kg of peptide. Schmaier teaches that an effective daily dose is 3g per day/70kg of body weight. This is equivalent to $4.3x10^{-8}$µg/day/kg. The amount taught by Schmaier is almost negligible. 0.04g/1Kg = 42mg/Kg The test under inherency is that following the disclosure, Schmaier, always inherently produces or results in the claimed invention. Such administration would not have any effect on NO production of the claimed invention, and consequently would not be effective in treatment of nitric oxide-mediated pathogenic conditions. One of ordinary skill would not be able to extrapolate such a dosage because as Schmaier discloses, the amount of BK analog is dependent on the degree of platelet aggregation inhibition desired. As stated by the Examiner the reference is silent with regard to the effect of the peptide on NOS therefore, one ordinarily skilled would not be able to correct for dosage because the effect, i.e., inhibition on NOS is not known. If the reference fails to teach the effects, it renders the invention non-obvious. Applicants respectfully request Examiner to withdraw this rejection.

III. Claim Rejections-35 U.S.C. § 103

Claims 1, 3, 5, 6, 9-11, 13, 15, and 16 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. 4152425(b) by Dietze et al. The Examiner states Dietze discloses infusion of 10-3000µg of kinin/L solution. The specifically preferred kinin is bradykinin. The infusion amount is exemplified at one liter. The Examiner further states, the use of up to 3000 µg/L/80 kg=37.5µg bradykinin/kg in the method of Dietze et al. would have been obvious because this is within the range of administration of bradykinin taught in the reference. Applicants respectfully traverse this rejection. To reject under 35 U.S.C. § 103, the Patent Office must establish a prima facia case of obviousness. In other words, the Patent Office must make a

factual showing that the claimed subject matter as a whole would have been obvious to a person of ordinary skill in the art to which that subject matter pertains at the time the invention was made. Moreover, a reference is said to teach away when a person of ordinary skill upon reading the reference would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that the applicant took. In re Gurley, 27 F. 3d 551, 31 USPQ 2d 1130, 1131 (Fed. Cir. 1994). Dietze et al. teaches away from the claimed subject matter because while Dietze et al. administers 500 μg of bradykinin, the infusion solution also contains phenothiazine (column 5, lines 49-56; column 8 lines 22-24), which when used over long periods of time is fairly toxic. In addition, Parkinsonism is a well-known side effect (See attachment). One of ordinary skill in the relevant art knows that Parkinsonism is a degenerative brain disorder. The condition is called Parkinson's disease when there is no apparent cause. Thus, one of ordinary skill who was looking to prevent or treat a nitric oxide-mediated pathogenic condition such as Parkinson's disease (see page 15 of specification), would not be inclined to use a reference like Dietze et al. because the infusion solution taught by Dietze et al. contains phenothiazine. It is well known that the treatment and prevention of such conditions can take place over a long period of time because diseases such as Parkinson's is degenerative. Thus, it is likely that side effects such as Parkinsonisms would develop.

In addition, phenothiazine, such as trifluoperazine binds to and inhibits calmodulin and has been used experimentally to block calcium/calmodulin-controlled reactions. (JM Lackie and JAT-Dow, The Dictionary of Cell and Molecular Biology, Academic Press, 3rd Ed., p.351 (2000)). Claims 10-11 reads in part "a method of preventing or treating a disease or condition in a mammalian subject that is effected by stimulation or inhibition of nitric oxide synthase, "wherein the nitric oxide synthase is nNOS-II." As disclosed inn the specification on page 13,

nNOS-II activity is calmodulin-dependent using L-arginine as a substrate. Thus, when using L-arginine as a substrate in the presence of a phenothiazine, such as trifluoperazine, would compete against the arginine substrate. This would have the effect of reducing the activity of nNOS-II. Again, one ordinarily skilled in the art would not use a reference like Dietze because it teaches away from the claimed embodiment(s) of the present invention, thus rendering the Applicants version of the invention non-obvious. Applicants respectfully request Examiner to withdraw this rejection.

Claims 1, 5, 6, 9-11, 15, and 16 were rejected under 35 USC 103(a) as being unpatentable over US 5648333[C], by Henke et al. The Examiner states, Henke et al. discloses the administration of the various peptides which are bradykinin antagonists in the range of 10μg-10mg/kg (col. 18, l. 25 and Table 1). Although the reference is silent with regard to the effects of the administration of bradykinin or arginine-containing peptides on NO production, it is reasonable to assume that the effects would be the same as claimed because the patient, the compounds administered, the dosage, and the mode of administration are the same; therefore, the result would inherently be the same. Applicants respectfully traverse this rejection.

The general rule is that inherency where and only where the consequence of following the reference disclosure always inherently produces or results in the claimed invention. See W.L. Gore Associates Inc. v. Garlock Inc., 220 USPQ 303, 314 (Fed. Cir. 1983), cert. denied, 469 US 851 (1984). "Inherency may not be established by probabilities or possibilities regarding what may have resulted in the prior art." In re Oelrich, 666 F.2d 578, 212 USPQ 323, 326 (CCPA 1981). The Examiner merely concludes it would be reasonable to assume that the effects would be the same. "[A]n examiner who relies on the theory of inherency 'must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent

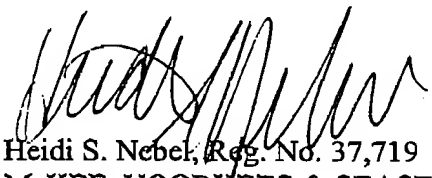
characteristic necessarily flows from the teachings of the applied prior art.'" Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Int. 1990). It would not be reasonable to assume that the administration of the various peptides which are bradykinin antagonists in the range of 10μg-10mg/kg would produce the same results as the claimed invention without knowing the effects of the bradykinin on the NO production. If the reference fails to teach the effects, it renders the invention non-obvious because one ordinarily skilled in the art would not refer to the reference. Part of solving a problem, especially in the biological sense is knowing what effects the variables have on the experiment. If one does not know the effect, one cannot measure its efficacy. An inherency rejection lacking such reasoning, fails to establish prima facie anticipation. Therefore, Henke et al. does not anticipate the claimed invention. Applicants respectfully request Examiner to withdraw this rejection.

IV. Conclusion

No fees or extensions of time are believed to be due in connection with this amendment; however, consider this a request for any extension inadvertently omitted, and charge any additional fees to Deposit Account No. 26-0084.

Reconsideration and allowance is respectfully requested.

Respectfully submitted,



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